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Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities

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Abstract. Vuorio A, Watts GF, Schneider WJ, Tsimikas S, Kovanen PT (Mehiläinen Airport Health Centre, Vantaa; University of Helsinki, Helsinki, Finland; University of Western Australia, Perth, Australia; Royal Perth Hospital, Perth, Australia; Medical University of Vienna, Vienna, Austria; University of California San Diego, La Jolla, CA, USA; Wihuri Research Institute, Helsinki, Finland). Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities (Review). *J Intern Med* 2020; **287**: 2–18.

There is compelling evidence that the elevated plasma lipoprotein(a) [Lp(a)] levels increase the risk of atherosclerotic cardiovascular disease (ASCVD) in the general population. Like low-density lipoprotein (LDL) particles, Lp(a) particles contain cholesterol and promote atherosclerosis. In addition, Lp(a) particles contain strongly proinflammatory oxidized phospholipids and a unique apoprotein, apo(a), which promotes the growth of an arterial thrombus. At least one in 250 individuals worldwide suffer from the heterozygous form of familial hypercholesterolemia (HeFH), a condition in which LDL-cholesterol (LDL-C) is significantly elevated since birth. FH-causing mutations in the LDL receptor gene demonstrate a clear gene-dosage effect on Lp(a) plasma concentrations and elevated Lp(a) levels are present in 30-50% of patients with HeFH. The cumulative burden of two genetically determined pro-atherogenic lipoproteins, LDL and Lp(a), is a potent driver of ASCVD in HeFH patients. Statins are the cornerstone of treatment of HeFH, but they do not lower the plasma concentrations of Lp(a). Emerging therapies effectively lower Lp(a) by as much as 90% using RNA-based approaches that target the transcriptional product of the *LPA* gene. We are now approaching the dawn of an era, in which permanent and significant lowering of the high cholesterol burden of HeFH patients can be achieved. If outcome trials of novel Lp(a)-lowering therapies prove to be safe and cost-effective, they will provide additional risk reduction needed to effectively treat HeFH and potentially lower the CVD risk in these high-risk patients even more than currently achieved with LDL-C lowering alone.

Keywords: atherosclerotic cardiovascular disease, burden, familial hypercholesterolemia, lipoprotein (a), therapy.

Introduction

In addition to 'traditional' atherosclerotic cardiovascular disease (ASCVD) risk factors, lipoprotein (a) [Lp(a)] has recently attracted much interest among clinicians focusing on improving the accuracy of cardiovascular risk stratification [1, 2]. Compelling evidence from traditional epidemiological, genomewide association and Mendelian randomization studies have revealed that elevated plasma Lp(a) levels increase the risk of acute myocardial infarction (AMI), ishemic stroke, calcific aortic valve disease and peripheral arterial disease in non-FH patients [3–8]. Even if LDL-C is lowered using currently available lipid-lowering therapies, a significant residual risk remains for individuals with elevated Lp(a), and specific therapies for Lp(a) are needed and likely to be available within next few years for clinical use [9–14]. It has been estimated that there are over 1.4 billion people worldwide with plasma Lp(a) levels over 50 mg dL^{-1} [15]. Given that approximately one

out of 250 individuals have HeFH [16], it can be calculated that there are at least 5 million HeFH patients worldwide with Lp(a) levels over 50 mg dL^{-1}. The overall prevalence of elevated Lp (a), defined as >50 mg dL^{-1} (>125 nmol L^{-1}), is shown in Fig. 1.

In this review, we first present the genetics of HeFH, then describe the significance of elevated Lp (a) in the general population as well as in HeFH and finally discuss the available and the near-future treatments for elevated Lp(a) and the need for new clinical guidelines in HeFH related to Lp(a). This review will not discuss the homozygous form of FH.

Familial hypercholesterolaemia

Familial hypercholesterolemia (FH) is the second most common, monogenic cause of inherited heart disease worldwide behind Lp(a). According to recent estimates, at least one in 250 individuals suffer from a life-long two- to-threefold elevation of serum low-density lipoprotein cholesterol (LDL-C) due to the heterozygous form of familial hypercholesterolemia (HeFH) [16–21].

Serum LDL-C levels in untreated HeFH children are typically above 4 mmol L^{-1} (150 mg dL^{-1}) [17]. In such patients, an increased carotid intima-media thickness is already detectable in the second decade of life [22–24]. If untreated, HeFH may lead to coronary stenoses in males with FH as young as 17 years, and in females as young as 25 years of age [25]. Such early-onset ASCVD can lead to an increased incidence of clinical events before middle age in adult HeFH patients [26]. Up to three quarters of HeFH patients may accumulate other CV risk factors, such as smoking and obesity, and this markedly heightens their risk of ASCVD [27].

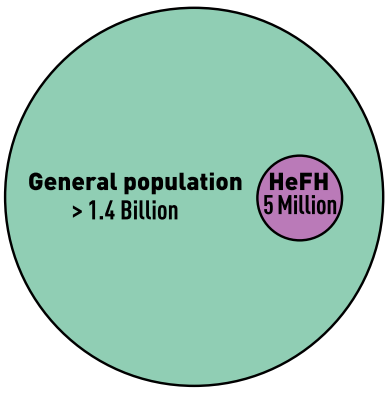

Fig. 1 *Estimated global numbers of elevated Lp(a) at >50 mg dL^{-1} (>125 nmol L^{-1}) and CVD risk. It has been estimated that there are over 1.4 billion people worldwide with serum Lp(a) levels over 50 mg dL^{-1} [15]. Given that about one out of 250 individuals have HeFH [16], then it can be calculated that there are at least 5 million HeFH patients worldwide with Lp(a) levels over 50 mg dL^{-1}. The overall prevalence of elevated Lp(a), defined as >50 mg dL^{-1} (>125 nmol L^{-1}).*

HeFH is caused by mutant alleles in the *LDLR, APOB* or *PCSK9* gene. Each of these genes encodes a specific protein that is involved in the clearance of LDL-C from the circulation. Approximately 90% of all HeFH cases are due to mutations in the *LDLR* gene [17]. As of 2016, over 1700 different *LDLR* mutations have been reported [28]. Interestingly, although more than 20 hypercholesterolemia-causing gain-of-function *PCSK9* variants have been found worldwide, in the United Kingdom, only one common *PCSK9* variant has been reported and this variant accounts for about 2% of the genetically identified HeFH patients [29]. Likewise, one variant of the *APOB* gene accounts for about 5%–10% of all HeFH cases in the European population [29]. Recently, additional *APOB* mutations were found to cause HeFH [30]. In populations lacking a founder effect, a mutation in *the LDLR, APOB* or *PCSK9* gene can be identified in less than half of the patients with clinically suspected HeFH [31]. For example, in the United Kingdom, the clinically suspected HeFH patients who are mutation-negative for *LDLR, APOB* or *PCSK9* genes, there is an accumulation of common small-effect LDL-C-raising alleles, which has been defined as 'polygenic HeFH' [32]. The most commonly used clinical criteria for the diagnosis of HeFH are the Dutch Lipid Clinic criteria [33] and the UK criteria [34].

LDL and Lp(a) particles

Low-density lipoproteins particles contain approximately 50% cholesterol mass by weight, with a lipid core consisting of cholesteryl esters (90%) and triglycerides (10%), while the surface of an LDL particle harbours a single copy of the apolipoprotein, apoB-100, embedded in a monolayer of phospholipid and unesterified cholesterol molecules [35]. The apoB-100 protein acts as a ligand for the LDL receptor and, accordingly, is crucial for the hepatic clearance of LDL particles [36]. ApoB-100 also mediates binding of LDL particles to proteoglycans within the arterial wall and thereby

leads to their retention and *in situ* modification, with ensuing development of atherosclerotic lesions [37].

Lp(a) particles resemble LDL particles, but crucially differ from those in that they contain one copy of a unique apoprotein, apoprotein(a) [apo(a)], which is linked via a disulphide bond to the apoB-100 moiety of the particle [38]. Apo(a) is a highly polymorphic glycoprotein synthesized and secreted almost exclusively by the liver [39]. It is noteworthy that there is a significant sequence homology (78%–100%) between apo(a) and the fibrinolytic pro-enzyme plasminogen [40, 41], in that both apo (a) and plasminogen contain loop-like structures called kringles [42, 43]. Interestingly, such kringle-like structures are also present in prothrombin and urokinase [44, 45]. However, the kringle types and copy numbers in apo(a) and in plasminogen are different. While plasminogen contains five different kringle structures (KI to KV), the apo(a) has lost KI, KII and KIII by deletion, harbours a single copy of KV, and most importantly, due to expansion and differentiation contains 10 different types of KIV ($KIV_{1–10}$), all of which have specific amino kringle compositions [41]. More precisely, the apo(a) isoforms harbour one copy each of KIV_1 and $KIV_{3–10}$, and from one to over 40 copies of KIV_2. Recently, it was found that high levels of Lp(a) corresponding low *LPA* KIV_2 number of repeats are associated with high risk of mortality in the general population [46].

The clinically available 'standard' LDL-C measurements actually determine the sum of cholesterol contained in both LDL and Lp(a) particles [47]. Thus, in subjects with very high Lp(a) levels (>1000 mg L^{-1}), the diagnosis of HeFH based solely on an LDL-C level may lead to a false positive classification [48]. For this reason, for example, a comprehensive genetic testing is the cornerstone of FH diagnostics, as it also affords an early and definitive diagnosis of HeFH and is cost-effective [49–51]. It has been also shown that systematic cascade testing of undiagnosed relatives of individuals with genetically diagnosed HeFH and elevated Lp(a) is effective [52, 53].

Elevated Lp(a) and the development of atherosclerotic and atherothrombotic cardiovascular disease

Understanding the role of Lp(a) in the formation and progression of atherosclerotic plaques, in arterial stenosis and in developing occlusions still poses scientific challenges which would lead to unambiguous conclusions [54–56]. This is because the role of Lp(a) as a risk factor is complicated by the fact that one cannot easily separate atherosclerotic effects from thromboses in the arterial system and by the fact that both the concentration of circulating Lp(a) particles and the apo(a) isoform size have been independently associated with ASCVD risk, although the majority of data is more in line of plasma Lp(a) being the key determinant [2].

The prevalence and risk cut-offs of Lp(a) as a risk factor for CHD may vary between ethnicities in the general population [57]. Guan et al. [58] in the MESA study followed a cohort of 1323 black, 1677 white, 548 Chinese American and 1044 Hispanics and recorded 235 CHD events in 8.5 years. Based on the data obtained, the cut-off for Lp(a) was different for white and Hispanic individuals compared to black individuals. The authors suggested an Lp(a) >30 mg dL^{-1} cut-off for blacks and whites, and an Lp(a) cut-off of >50 mg dL^{-1} for Hispanics. In a very recent study, in which Lp(a)-associated risk of the development of carotid plaques was analysed, it was found that carotid plaque burden was greater in whites than in blacks, whereas in Hispanics, the results were borderline [59]. However, in other similarly powered studies such as the Dallas Heart Study and the ARIC study, elevated Lp(a) was similarly potent as a risk factor. Within these variabilities, the overall data can be interpreted that elevated Lp(a) (>50 mg dL^{-1} or >~125 nmol L^{-1}) is similarly a risk factor for CHD irrespective of racial make-up [60, 61]. However, within different racial groups, it is more likely to find more patients with elevated Lp(a) in Blacks, South Asians, Caucasians, Hispanics and East Asians, in that order [15].

A significant consequence of the structural similarity between apo(a) and plasminogen, as described above, is that apo(a) may competitively inhibit the activation of plasminogen; that is, it possesses antifibrinolytic activity, which in turn may explain the potential role of the lipoprotein as a mediator of increased atherothrombotic risk [62]. Thus, since Lp(a) is both a cholesterol carrier into the arterial wall and possesses antifibrinolytic activity, it may constitute a link between atherosclerosis and atherothrombosis [55]. Furthermore, Lp(a) has been reported to enhance oxidative stress [63, 64] and is associated with endothelial dysfunction [65–67]. Impaired

endothelium-dependent dilation has been shown to be present in HeFH children as young as 7 years of age, and this impairment was associated with the Lp(a) concentration [68]. Finally, the atherogenicity of Lp(a) lipoprotein can partly mediated by its content of pro-inflammatory oxidized phospholipids, which appear to be responsible for monocyte activation, adhesion to endothelial cells and release of pro-inflammatory cytokines [69]. Furthermore, since Lp(a) is enriched in platelet-activating factor, the particles can promote platelet aggregation [70, 71]. In summary, since Lp(a) particles contain, in addition to the proatherogenic components of LDL, also apo(a), they are likely more atherothrombogenic than LDL particles [2, 72].

Analytical issues with measurement of Lp(a)

Lp(a) concentrations are relatively infrequently measured in routine clinical care [73]. Nonetheless, the measurement of Lp(a) needs to be well standardized [74]. Additionally, familial combined hyperlipidemia (FCHL) and elevated lipoprotein(a) [Lp(a)] may mimic HeFH [75].

Apo(a) isoform size variations pose significant issues for the reliable estimation of *bona fide* Lp (a) concentrations. In a recent round table meeting, Dr. Marcovina pointed out that Lp(a) values in samples with small apo(a) isoforms, smaller than the isoforms in the calibrator, are underestimated and the values in samples with isoforms larger than those in the calibrator are actually overestimated [76]. Accordingly, Lp(a) mass assays have limitations because Lp(a) particles are heterogenous in size. However, the currently available assays for routine clinical care which are linked to World Health Organization and International Federation of Clinical Chemistry and Laboratory Medicine standards are able to detect those individuals having Lp(a) levels over 50 mg dL^{-1}, so that identifying individuals at highest risk is not a clinical problem [2]. However, increased accuracy is required so as not to misclassify individuals with borderline levels (30–50 mg dL^{-1} or 75–125 nmol L^{-1}). Additionally, sample handling and storage conditions are of utmost important [74]. It can be concluded that internationally harmonized guidelines must be put in place to ensure reliability and high quality in Lp(a) measurement going forward [15].

Elevated lipoprotein(a) levels in familial hypercholesterolemia

Since all HeFH patients are high-risk patients, even moderate increases in Lp(a), that is to concentrations ranging from 30 to 50 mg dL^{-1}, may further enhance their ASCVD risk as an independent risk factor for ASCVD (Fig. 2) [77]. It has been also shown that plasma Lp(a) concentration is elevated in HeFH compared to the general population (Table 1). Indeed, it has been recently pointed out that the risk of ASCVD starts to increase already at plasma concentrations above 30 mg dL^{-1} [78]. In an earlier report by Carmena and coworkers studied 98 HeFH subjects and 66 healthy first- and second-degree relatives from 30

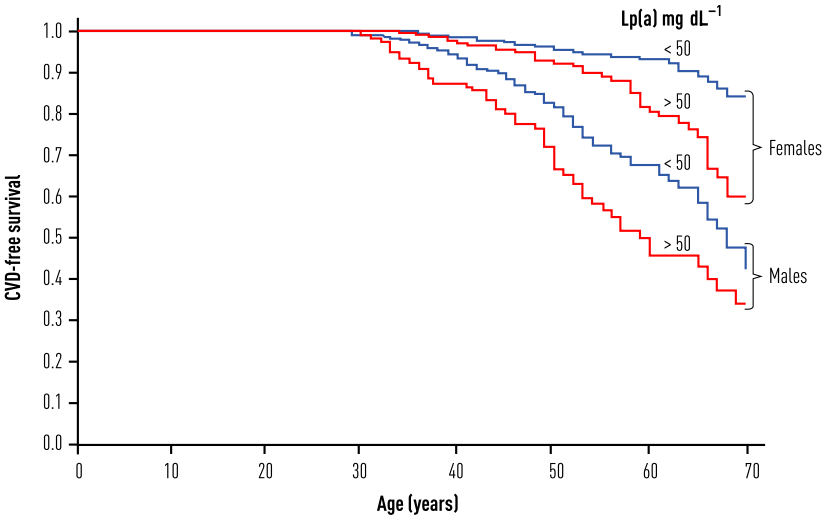

Fig. 2 *Kaplan–Meier curves for cardiovascular disease-free survival in patients with HeFH based on Lp(a) concentrations and gender. Adopted from [77].*

Table 1. *Selected studies supporting the observation that serum Lp(a) is elevated in genetically diagnosed HeFH*

Lp(a) concentration mg dL^{-1} in controls/ number of studied individuals	Lp(a) concentration mg dL^{-1} in HeFH/ number of studied individuals	*P*-value	References
21.0 (7–47.2)/1969	23.6 (9.6–59.2)/957	<0.0001	[77]
11.8 (6.5–29.4)/4015	21.9 (10.0–34.2)/198[a]	2.1×10^{-7}	[145]
	21.1 (11.7–34.9)/42[b]	1.1×10^{-3}	

[a]LDLR mutation.
[b]PCSK9 mutation.

families with FH caused by the French-Canadian >10-kb deletion in the LDL receptor gene [79]. The authors used the threshold value of 20 mg dL^{-1} for Lp(a) to separate HeFH patients in the groups with CHD and without CHD. It was demonstrated that the prevalence of CHD in HeFH patients with Lp(a) values ≤20 mg dL^{-1} was not significantly different from that in HeFH patients with values above that level.

Receptors potentially involved in Lp(a) catabolism

It has been shown that HeFH patients with LDL-receptor null mutations, which lead to complete absence of LDL receptors, tend to have higher Lp(a) concentrations compared with HeFH patients with mutations leading to partially inactive LDL receptors [77]. Moreover, in FH families, the homozygous FH patients, that is those having two nonfunctional LDL receptor alleles, the Lp(a) levels were found to be almost twofold higher than in the FH heterozygotes [80]. Thus, the FH-causing mutations in the LDL receptor gene demonstrate a clear gene-dosage effect on Lp(a) plasma concentrations.

Besides the LDL receptors, there are several other classes of receptors potentially involved in Lp(a) catabolism (Fig. 3) [81]. Interestingly, of the two different pharamaceuticals with an ability to increase hepatic LDL receptor numbers, PCSK9 inhibitors decrease the plasma concentrations of Lp(a), while statins fail to do so. In fact, a recent, subject-level meta-analysis of 53256 subjects showed that statins may increase mean Lp(a) levels from 8% to 24%. Although statins have been documented to improve outcomes in most clinical subsets, the effect of these increases in subjects with already elevated Lp(a) is not known [82]. The multiplicity of hepatic catabolic routes for Lp(a) may help us to understand this apparent paradox. Moreover, it has been shown that during statin-induced low LDL levels, Lp(a) internalization depends on PCSK9 activity [83], a finding which implies that the LDL receptors are involved in the catabolism of Lp(a). It is also possible that Lp(a) is a competitive ligand for the LDL receptor especially when LDL-C levels are very low, which occurs during a treatment regimen in which PCSK9

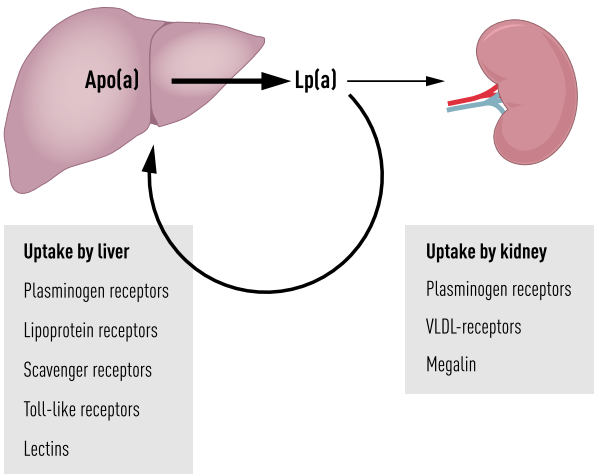

Fig. 3 *Schematic representation of proposed potential pathways for receptor mediated lipoprotein(a) catabolism in the human body. Circulating Lp(a) is derived from apolipoprotein(a) that is synthesized and secreted by the liver. The assembly of an Lp(a) particle may occur either before and after secretion of apolipoprotein(a), that is within the hepatocytes, at the hepatocyte surface, or in the circulating blood, respectively. The proposed multiple receptor-mediated routes of Lp(a) removal from the circulation are shown. The liver is considered to play the major role in Lp(a) catabolism, while the kidneys appear only to contribute to Lp(a) clearance. Peripheral tissues may also contribute to receptor-mediated removal of Lp(a) from the circulation, but their contribution to the regulation of the circulating Lp(a) level appears unlikely [81, 143].*

inhibitors are given in combination with a statin [84, 85].

Other issues related Lp(a) and ASCVD risk in HeFH

Another issue to be considered is that the Lp(a) distribution is highly skewed rightward with a wide range from 0 to about 300 mg dL^{-1} [1]. Thus, in the worst risk scenario, a high-risk HeFH patient may have an extremely highly elevated CHD risk due to lifelong elevated level of very high Lp(a).

Among HeFH patients, the time of the onset of subclinical or clinical CHD varies, and this observation is only partly explained by variations in the traditional risk factors [86]. Clearly, for improved accuracy and a higher precision in risk assessment of this patient group, other genetic biomarkers for ASCVD besides LDL-C level are needed. Lp(a) is of even greater significance among HeFH patients than in the general population because all HeFH patients are already high-risk patients due to their high LDL-C burden. The elevation of Lp(a) in HeFH creates a unique situation in which two genetically determined proatherogenic factors, namely Lp(a) and LDL-C, are exerting a lifelong cardiovascular risk burden for atherosclerosis [87, 88]. Moreover, it is of particular importance that significantly elevated Lp(a) levels are more prevalent among HeFH patients than in the general population [77]. Thus, as noted above, in a recent very large study, about one-third of HeFH patients were reported to have an elevated concentration of Lp(a), defined as >50 mg dL^{-1} [89]. Moreover, plasma Lp(a) levels above 100 mg dL^{-1} have been found in approximately 5% of patients with HeFH, while in non-FH hypercholesterolemic patients, the corresponding value was about half of it (2.6%) [90].

Elevated Lp(a) levels have been associated with aortic valve calcification (AVC) in HeFH. In a study of 129 asymptomatic 40- to 69-year-old HeFH patients whose plasma Lp(a) was evaluated as a possible risk factor for coronary artery calcification (CAC) and aortic valve calcification (AVC), plasma Lp(a) concentration emerged as an independent risk indicator for AVC, but not for CAC [91]. The authors concluded that Lp(a) concentration could be useful as a risk marker for AVC in HeFH.

In an association study of 191 statin-treated HeFH patients (50% male; 48 ± 15 years) divided into two groups according to the Lp(a) level being either below or above 30 mg dL^{-1}, the presence or absence of carotid plaques and the thickness of carotid intima-media were determined by ultrasonography [92]. Interestingly, in these statin-treated HeFH patients, the plasma LDL-C level was 3.23 ± 1.02 mmol L^{-1} and 3.20 ± 0.85 mmol L^{-1} in the low (<30 mg mL^{-1}) and high (>30 mg mL^{-1}) Lp(a) group, respectively, but the Lp(a) levels were neither associated with the presence or absence of carotid plaques, nor did the levels correlate with carotid intima media thickness. Therefore, the authors concluded that adequate statin treatment may delay carotid atherosclerosis in HeFH, and if it does, then the effect does not depend on Lp(a) levels. Based on above findings, we conclude that Lp(a) is a genetic risk factor for atherosclerotic cardiovascular disease with particular significance in HeFH, since in such patients, the combination of two lifelong proatherogenic cardiovascular risk factors, Lp(a) and LDL-C, is deleterious [93].

Despite the consensus that elevated Lp(a) is a risk for ASCVD, the recommendations for risk-level cut-offs vary. The European Atherosclerosis Society proposes that, for preventative purposes, the Lp(a) levels should be less than 50 mg dL^{-1} [1]. The Canadian Cardiovascular Society, in turn, recommends an appropriate cut-off point of 30 mg dL^{-1} [94]. Because HeFH patients are already at elevated risk for ASCVD due to their lifelong elevated plasma LDL-C level, it would be appropriate to apply the more rigorous Canadian Atherosclerosis Society recommendation to the HeFH patients. Thus, more investigations are clearly needed to establish a valid Lp(a) cut-off level for HeFH patients, all of whom possess an Lp(a)-specific increased risk of developing premature ASCVD [91]. More rigorous cut-off values would reflect the reasoning in the guidelines recommending more stringent LDL-cholesterol target levels in HeFH than in the general population.

Current treatment of LDL-cholesterol in HeFH and its effect on Lp (a)

Statin treatment and LDL-cholesterol

Because of the premature atherosclerosis in HeFH, a lifelong statin treatment beginning already in childhood is the current clinical practice [51, 95]. Indeed, current guidelines recommend that statin treatment should be started in HeFH children between 8 and 14 years of age [50, 96–101]. Importantly, statins have been found to be effective in lowering LDL-C levels in HeFH children, and

their safety has been demonstrated in over one thousand HeFH children participating in placebo-controlled studies of statin treatment. In such studies, the difference in the mean relative reductions of LDL-C levels between statin-treated and placebo-treated cohorts was 32% at the end of the follow-up [95]. In HeFH children, the serum LDL-C target is <3.5 mmol L^{-1} (135 mg dL^{-1}), when the children reach adulthood, their statin treatment needs to be intensified and, whenever necessary, to be combined with the cholesterol-absorption inhibitor ezetimibe to reach the serum LDL-C target of <2.5 mmol L^{-1} (100 mg dL^{-1}) [17].

PCSK9 inhibitor treatment and LDL-cholesterol

For adult patients with HeFH and with known ASCVD, the serum LDL-C target is <1.4 mmol L^{-1} (<55 mg dL^{-1}) [17, 102–104]. For adult HeFH patients with known ASCVD, i.e., at very-high risk, there is a new treatment option: a statin, with or without ezetimibe, combined with a PCSK9 inhibitor. The inhibitor, either alone or in combination with a statin, lowers LDL-C levels approximately by 60% both in non-HeFH and FH patients [105–110]. In fact, the combination of a statin and a PCSK9 inhibitor allows to reach serum LDL-C levels lower than 1.4 mmol L^{-1} (55 mg dL^{-1}) even in HeFH patients. In practice, however, many FH patients fail to reach such stringent goal, as shown in a recent study [109], in which the efficacy of the PSCK9 inhibitor alirocumab in HeFH was studied. This 24-week-long placebo-controlled study included 35 controls and 72 HeFH patients, who were either fulfilling the clinical Simon Broome Criteria or had been genotyped for HeFH [109], and who received 150 mg of alirocumab every two weeks, in addition to a tolerated maximal statin treatment. In this study, in total, only 41% of the high-risk and the very-high-risk HeFH patients reached the less stringent goals defined for such patients at that time. This trial reveals how challenging it may be to reach LDL-C goals in HeFH patients even with the newly available highly efficient therapies under extremely well-controlled conditions in a clinical study.

Statin treatment and lipoprotein(a)

A recent review of the mechanisms underlying the catabolism of Lp(a) [81] concisely addressed the differences between the catabolic routes of Lp(a) particles and that those of LDL particles. In contrast to LDL-lowering therapies, where multiple approaches targeting one highly specific receptor have effectively been used to lower LDL, the authors considered it more likely that for Lp(a), it will be a matter of multiple therapies targeting multiple receptors on the surface of liver cells. A large number of studies provide evidence that these receptors fall into five main categories, namely 'classical' lipoprotein receptors, toll-like receptors, scavenger receptors, glycoprotein receptors (lectins) and plasminogen receptors (Fig. 3). Unfortunately, statins which have been the cornerstone medication in HeFH for decades, upregulate the hepatic LDL-receptors without having an effect on serum concentration on Lp(a) [111].

One aspect that should be kept in mind is that statins may increase Lp(a) levels in children with HeFH. For example, Rodenburg et al showed that pravastatin increased Lp(a) 21.9% following initiation of statin therapy [112]. Despite these limitations of statins, statins benefit all subgroups of patients, including those with elevated Lp(a), and should be used as first line in patients with HeFH.

PCSK9 inhibition and lipoprotein(a)

PCSK9 inhibition on top of high-intensity statin treatment is suitable for HeFH patients because it lowers not only the concentration of LDL-C but also that of Lp(a) [111, 113]. Although PCSK9 inhibition lowers the concentration of Lp(a) by 15%–30%, such relative drop is not enough when the baseline level of Lp(a) is high [114]. Disappointingly, when evolocumab was studied in a study where all patients had elevated Lp(a) >50 mg dL^{-1}, only a 14% reduction was noted [115]. In this recent multicenter randomized placebo-controlled study, 129 hypercholesterolemic patients whose median baseline levels of Lp(a) and LDL-C were 200 nmol L^{-1} (80 mg dL^{-1}) and 3.7 mmol L^{-1}, respectively, were randomized to monthly evolocumab 420 mg or placebo for a duration of 4 months. Compared with placebo, evolocumab treatment reduced, on average, the Lp(a) and LDL-C level by 14% and 61%, respectively, but failed to significantly reduce arterial wall inflammation. As the authors speculated, the persistently elevated levels of Lp(a) may have contributed to the unaltered arterial wall inflammation. This study brings forth that even effective LDL-C-lowering pharmacotherapies specifically enhancing the activity of hepatic LDL receptors are not sufficient for an effective lowering of Lp(a) level. Moreover, the lack of association of Lp(a) levels with the activity of any one of

the receptors proposed to mediate hepatic removal of Lp(a) [81] supports the notion that Lp(a) clearance is mediated by multiple receptors (Fig. 3). In such scenario, targeting receptor-mediated removal of circulating Lp(a) particles for therapy may indeed require a complex approach. Thus, rather than concentrating on Lp(a) clearance, recent efforts have been targeted at reducing the hepatic production rate of apo(a).

Strategies to lower Lp(a) concentrations

As a rule, plasma Lp(a) levels are not responsive to dietary changes. Although a significantly increased Lp(a) requires medical treatment, adherence to ideal cardiovascular risk behaviours, such as nonsmoking, maintenance of a desirable body weight and regular physical activity may reduce the Lp(a)-associated risk of ASCVD [116].

Currently available drugs

Some drugs can lower both LDL-C and Lp(a) (Table 2). This is a significant therapeutic gain as Lp(a) acts synergistically with elevated LDL-C as a risk factor for ASCVD [117]. Of the available drugs, the cholesteryl ester transfer protein (CETP) inhibitors lower plasma Lp(a) concentrations by 20%–40% [118–120]. Additionally, hormonal therapy, like thyromimetics, such as eprotirome, decreases Lp(a) levels by 20%–40%, and oestrogen lowers Lp(a) by about 24% [111]. Mipomersen, which is used in homozygous FH, lowers Lp(a) approximately −25% [121].

Lipoprotein apheresis

Lipoprotein apheresis is a therapeutic approach that effectively lowers both serum LDL-C and Lp(a), or selectively Lp(a) from the plasma. In Germany, lipoprotein apheresis is indicated for severely hypercholesterolemic patients with controlled LDL-C in whom progression of atherosclerosis is documented and who are at very high risk of cardiovascular events, and also for patients with plasma Lp(a) >60 mg dL^{-1} associated with progressive CHD. The German Lipoprotein Apheresis Registry was launched 2011, and data acquired during the time period 2012–2015 were recently published [122]. Over this period, 68 German apheresis centres collected data of 1283 patients suffering from progressive cardiovascular disease and undergoing lipoprotein apheresis treatment of high LDL-C levels and/or high Lp(a) levels. A total of 15 167 individual treatment sessions were investigated, and analysis of the results revealed an acute median LDL-C reduction of 69% and a median Lp(a) reduction of 70% among treated patients. It is to be emphasized that because of rapid production of Lp(a) in the liver, the levels return to baseline and the time-averaged reduction between sessions is only ~35% [123]. Patient data were compared regarding the incidence rate of coronary events 1 and 2 years before the start of treatment and during 1 year on treatment. During the first year of treatment, a remarkable 97% reduction of coronary events was found.

In the prospective multicentre Pro(a) Life Study, 170 patients who had Lp(a) hyperlipoproteinemia and progressive cardiovascular disease despite maximally tolerated lipid-lowering treatment were investigated [124]. A subgroup analysis of this study, stratified by LDL-C concentration, suggested a reduction of coronary events related to selective Lp(a) apheresis. Additionally, selective Lp(a) apheresis in patients with plasma Lp(a) levels over 50 mg dL^{-1} leads to regression of both carotid and coronary atherosclerosis against background statin therapy [124–126]. LDL apheresis also significantly lowers plasma oxidized phospholipids, which may also play a role in its pleiotropic beneficial effects [127].

RNA-based drugs

Since Lp(a) is synthesized in hepatocytes, liver-targeted agents that reduce the synthesis of apo(a)

Table 2. *Effect of various therapies on serum Lp(a) and LDL-C concentrations*

Drug	Lp(a) lowering	LDL-C lowering	References
Niacin	−23%	−13%	[146]
Apheresis	−70% acutely, mean −35%	Up to 75%	[124, 147]
CETP inhibitors	−20 to −40%	−20 to 40%	[120, 148]
PCSK9 inhibitors	−15 to −30%	−50 to 60%	[106, 107, 114, 115, 149]
Apo(a) antisense oligonucleotides	−70 to −90%	−10 to 20%	[128, 131, 133]

have the most promise in substantially lowering plasma Lp(a). In fact, this has been achieved by using antisense oligonucleotides (ASOs) directed to apo(a) [128–131]. ASOs are single-stranded strings of modified DNA that are usually 13–20 nucleic acids long and are designed to be complementary to a site on the mRNA target, in this case *LPA* mRNA [132]. After binding to *LPA* mRNA to create a double-stranded molecule, RNAase H1 is recruited to the complex and cleaves the sense strand, allowing the antisense molecule to bind another sense strand and the process is repeated. For this reason, these molecules have a half-life of 2–4 weeks, allowing longer dosing intervals.

Using a liver-targeted ASO containing N-acetylgalactosamine that is directed to the hepatocyte asialoglycoprotein receptor, a dose-dependent mean reduction in Lp(a) was noted at 68%, 80% and 92% reduction with 10, 20 and 40 mg IONIS-APO(a)-L_{Rx}, respectively, in otherwise healthy subjects with elevated Lp(a) (Fig. 4) [131]. A randomized, double-blind, placebo-controlled, dose-ranging trial that enrolled 286 patients with established cardiovascular disease and Lp(a) ≥60 mg dL^{-1} (≥150 nmol L^{-1}) was recently reported [133]. Mean baseline Lp(a) levels among the six groups in this study were 234–280 nmol L^{-1}. AKCEA-APO(a)-L_{Rx} (formerly IONIS-APO(a)-L_{Rx}) resulted in dose-dependent decreases in Lp(a) of 35% at 20 mg/4 weeks, 56% at 40 mg/4 weeks, 58% at 20 mg/every 2 weeks, 72% at 60 mg/4 weeks and 80% at 20 mg/week, versus 6% decrease with placebo (*P* value range: 0.003 to <0.0001 versus placebo). In this study, approximately one third of the patients were HeFH patients who were adequately treated with moderate- to high-dose statins (>80%), ezetimibe (~50%) and PCSK9 inhibitors (~20%). In addition to robust Lp(a) reduction, additional 16% and 11% reductions were noted in LDL-C and apoB, respectively, on top of the baseline LDL-C-lowering therapy.

In addition to the ASOs, other approaches are being developed for an efficient reduction of plasma Lp(a) concentration. One such attempt is the generation of small-interfering RNAs (siRNAs) that specifically block the hepatic synthesis of apo(a) [134].

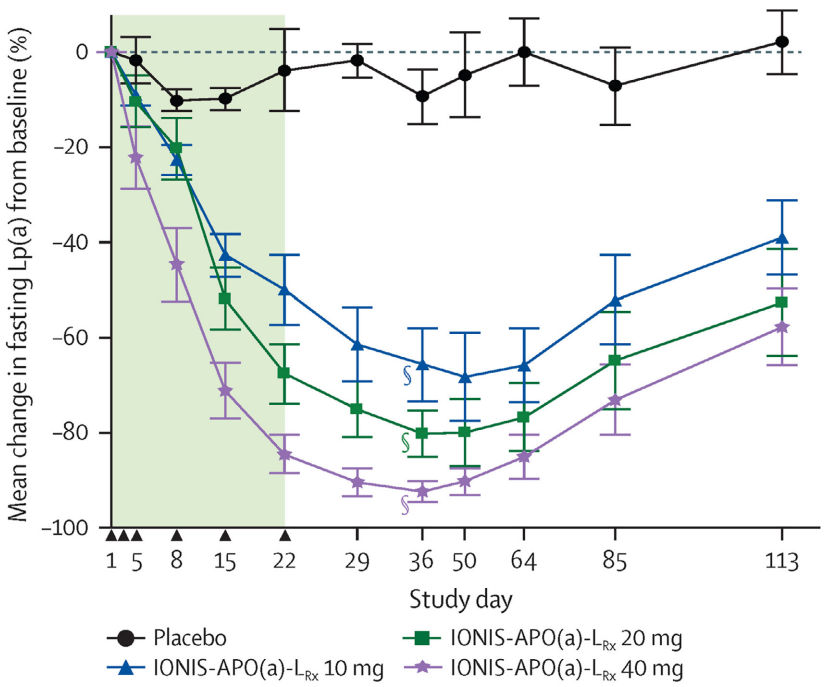

Fig. 4 *Mean percentage change in Lp(a) concentration in the IONIS-APO(a)-L_{Rx} trial in the multiple ascending dose phases. Adopted from [131]. Using a liver-targeted ASO containing N-acetylgalactosamine that is directed to the hepatocyte asialoglycoprotein receptor, a dose-dependent mean reduction in Lp(a) was noted at 68%, 80% and 92% reduction with 10, 20 and 40 mg IONIS-APO(a)-L_{Rx}, respectively, in otherwise healthy subjects with elevated Lp(a).*

Table 3. *Recent existing HeFH guidelines and Lp(a)*

Guideline	Recommendation	References
International FH Foundation	Although FH is a life-time coronary risk equivalent, patients should be assessed for additional major cardiovascular risk factors, including lipoprotein (a)	[135]
Canadian Cardiovascular Society	We suggest that conventional risk factors such as age, sex, HDL-C, hypertension, smoking, lipoprotein(a) and diabetes be ascertained in patients with FH (weak evidence).	[136]
Hong Kong Expert Panel Consensus	Other risk factors such as Lp(a) are also important	[137]
American Heart Association	Not mentioned	[138]
Japan Atherosclerosis Society	Not mentioned	[139]
National Institute of Health and Care Excellence	Not mentioned	[50]

Towards new clinical practice guidelines

Currently, the value of mitigating the combined risk caused by highly elevated serum LDL-C and elevated Lp(a) in HeFH patients with elevated Lp(a) is not adequately recognized in clinical practice. This gap in awareness may soon be filled with the availability of new RNA-based therapies that selectively inhibit the synthesis and production of Lp(a) particles.

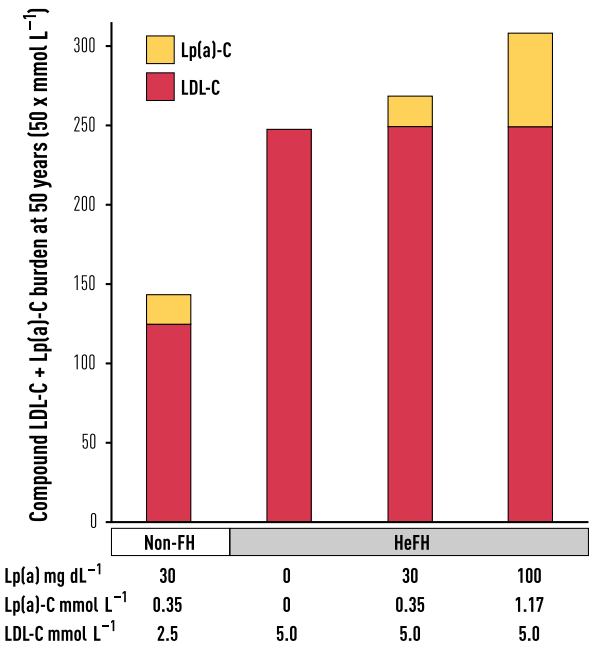

Fig. 5 *Cumulative burden of LDL-cholesterol + Lp(a)-cholesterol. To emphasize the significant role of Lp(a), we propose the risk concept of the cumulative burden of LDL-C + Lp(a)-cholesterol [Lp(a)-C] life years, based on the notion that Lp(a) is a low-density lipoprotein (LDL)-like particle consisting of 45% cholesterol [140]. In this figure, the burden at the age of 50 years is shown.*

The potential role of elevated Lp(a) in risk stratification has been acknowledged in some guidelines on the management of HeFH [135–137], but in not in others [50, 138, 139] (Table 3). Once an efficient treatment of elevated Lp(a) becomes widely available, there will be a requirement not only for risk estimation including the Lp(a)-specific contribution to total CV risk, but also for guiding the clinicians to properly monitor the efficacy and safety of the treatment of elevated Lp(a). The recent clinical studies in which Lp(a) has been robustly lowered, that is showing about 70%–90% Lp(a) lowering [128–131], are a clear testimony of the need to consider robust, long-term Lp(a) treatment in HeFH, particularly if the new therapies are proven to be safe and cost-effective in clinical outcome trials.

To illustrate the impactful role of Lp(a), we propose the risk concept of the cumulative LDL-C + Lp(a)-cholesterol [Lp(a)-C] life years, based on the notion that Lp(a) is a low-density lipoprotein (LDL)-like particle consisting of 45% cholesterol [140] (Fig. 5). In this illustration, the cumulative burden of LDL-C + Lp(a)-C at the age of 50 yrs in a non-FH individual and in three non-treated HeFH patients are shown. Figure 6 is a schematic representation of cumulative burden of LDL-cholesterol- and Lp

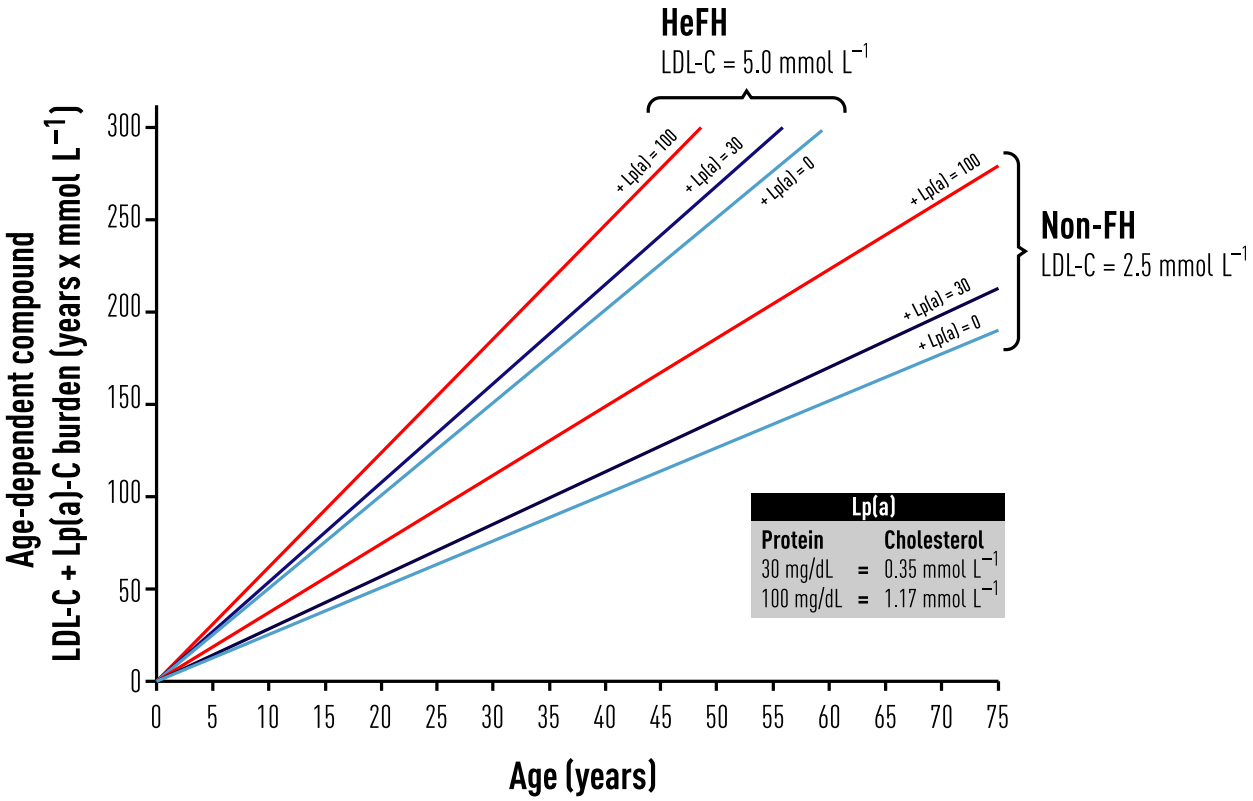

Fig. 6 *Schematic representation of cumulative burden of LDL-cholesterol- and Lp(a)-cholesterol. Cumulative burden of LDL-C + Lp(a)-C illustrated as a function of age in non-FH individuals (LDL-C = 2.5 mmol L^{-1}) and in untreated HeFH patients (LDL-C = 5.0 mmol L^{-1}). In both groups the effects of three different Lp(a)-burdens are shown.*

(a)-cholesterol. The cumulative burden of LDL-C + Lp(a)-C illustrated as a function of age in non-FH individuals (LDL-C = 2.5 mmol L^{-1}) and in untreated He-FH patients (LDL-C = 5.0 mmol L^{-1}). In both groups the effects of three different Lp(a)-burdens are shown. This illustration shows the need to also treat Lp(a) independently even if the LDL-C level is 2.5 mmol L^{-1}. It also illustrates that effective lowering of LDL-C can compensate for the currently available only modest lowering of high Lp(a) levels. However, this approximation only takes account the cholesterol content of Lp(a), but not the other pro-atherosclerotic, pro-thrombotic and pro-inflammatory features of Lp(a).

Additionally, here we present the concept of the compound LDL-cholesterol and Lp(a)-particle cholesterol burden to facilitate the incorporation of Lp(a) as a clinically useful risk assessment tool (Fig. 7). Using this tool, we demonstrate the clinical impact of high serum Lp(a) concentration (100 mg dL^{-1}) compared to currently recommended upper limit for serum Lp(a) concentration (30 mg dL^{-1}) in untreated HeFH patients. Lp(a) particle burden is converted to LDL-C burden based on the fact that reductions in Lp(a) of approximately 100 mg dL^{-1} are needed to reduce the risk of CHD similar to that achieved by lowering LDL-C level by 1 mmol L^{-1} [144]. This cumulative compound LDL-C and equivalent Lp(a) particle years burden defines the age-dependent burden of the coronary arterial wall to compound LDL-C and Lp(a) (years × mmol L^{-1}). We have earlier presented separately LDL-C-years burden [141] and Lp(a)-years burden [10]. When comparing the threshold burden for CHD [17], it can be demonstrated that untreated HeFH patients having serum Lp(a) concentration of 100 mg dL^{-1} reach the CHD threshold burden about 4 years earlier compared to untreated HeFH patients with serum Lp(a) concentration of 30 mg dL^{-1}.

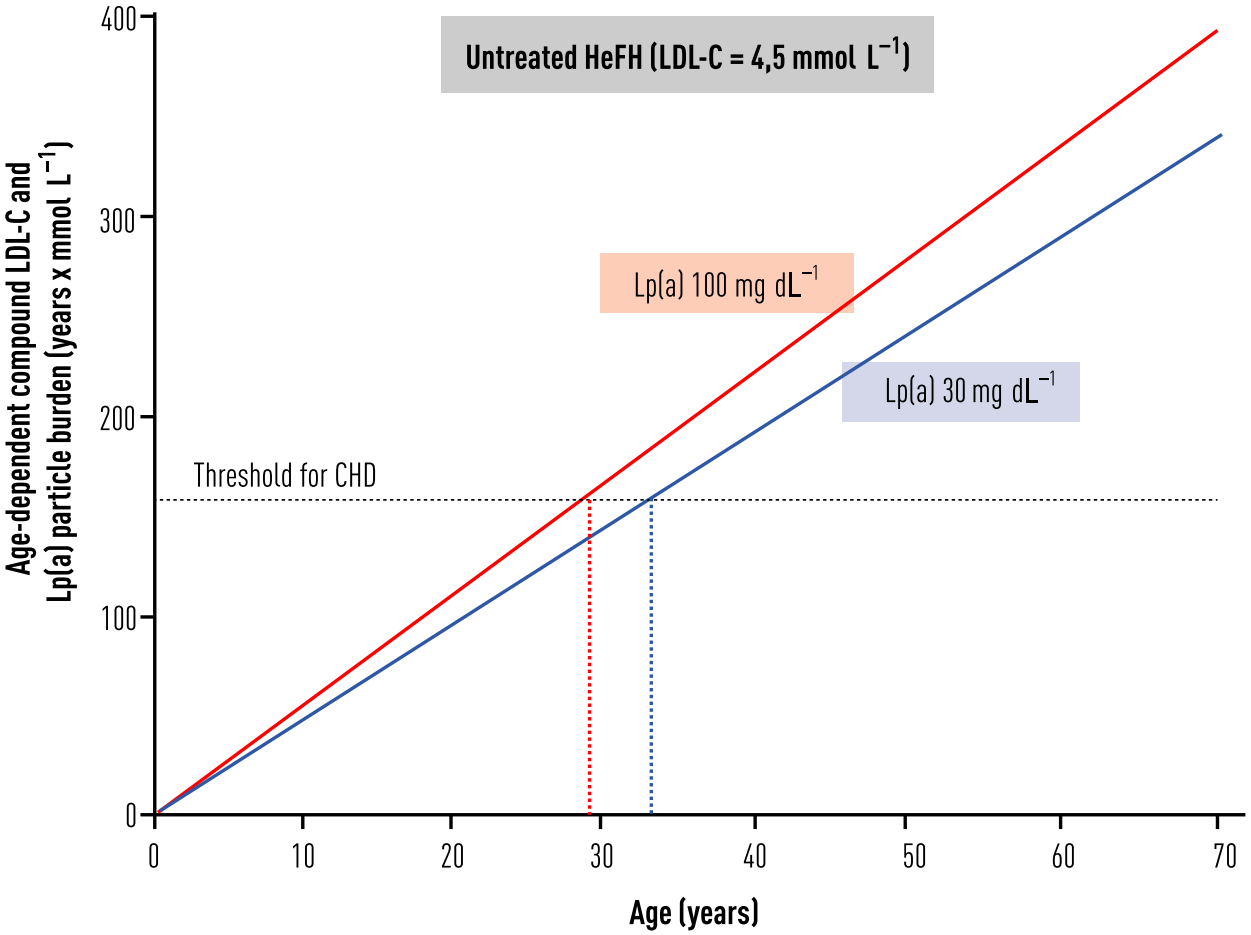

Fig. 7 *Schematic representation of compound LDL-cholesterol and Lp(a) particle burden. We generated the concept of the compound LDL-cholesterol and Lp(a)-particle cholesterol burden to facilitate the incorporation of Lp(a) as a clinically useful risk assessment tool. Using this tool, we demonstrate the clinical impact of high serum Lp(a) concentration (100 mg dL^{-1}) compared to currently recommended upper limit for serum Lp(a) concentration (30 mg dL^{-1}) in untreated HeFH patients. Lp(a) particle burden is converted to LDL-C burden based on the fact that reductions in Lp(a) of approximately 100 mg dL^{-1} are needed to reduce the risk of CHD similar to that achieved by lowering LDL-C level by 1 mmol L^{-1} [144]. This cumulative compound LDL-C and equivalent Lp(a) particle years burden defines the age-dependent burden of the coronary arterial wall to compound LDL-C and Lp(a) (years × mmol L^{-1}). We have earlier presented separately LDL-C-years burden [141] and Lp(a)-years burden [10]. When comparing the threshold burden for CHD [17], it can be demonstrated that untreated HeFH patients having serum Lp(a) concentration of 100 mg dL^{-1} reaches the CHD threshold burden about 4 years earlier compared to untreated HeFH patients with serum Lp(a) concentration of 30 mg dL^{-1}.*

From a clinical perspective, future HeFH guidelines should define a threshold level for the initiation of the treatment and also the target level for Lp(a) concentration. The European Atherosclerosis Society suggests that the Lp(a) levels for preventative purposes are <50 mg dL^{-1} [103]. The Canadian Cardiovascular Society recommends a lower cut-off point of 30 mg dL^{-1} [94]. Because the adult HeFH patients are already at elevated risk of CHD due to their lifelong elevated serum LDL-C level, it would be appropriate to apply for the Lp(a) level the more rigorous Canadian Atherosclerosis Society 30 mg dL^{-1} target level recommendation, which is reachable with the modern pharmacotherapy of Lp(a).

Conclusion and future perspectives

The importance of Lp(a) as a causal risk factor for ASCVD has experienced a renaissance derived

from new genetic studies and particularly from the availability of RNA-based therapies that lower the plasma concentrations of Lp(a) by more than 80% [15]. Concurrently, there is an intensive development of new and effective Lp(a) treatments based on ASOs and siRNAs. Among the target patient populations, HeFH patients with a well-grounded high risk of ASCVD constitute an important subgroup in whom effective Lp(a)-lowering will offer possibility to still improve the prognosis of the disease beyond the current new therapies that can markedly reduce serum LDL-C concentrations. There is clearly a demand to update current FH clinical practice guidelines as soon as clinical trials prove the safety and cost-effectiveness of Lp(a) lowering. It is very likely that the benefits of the novel and efficient Lp(a)-lowering therapies will be analogous to those of robust LDL-C lowering, for they are dependent on the impact of the absolute magnitude of Lp(a) lowering on a lifelong burden ASCVD related to an elevated Lp(a) level [10, 142].

Conflict of interest statement

GFW has received research grants and honoraria for lectures and advisory boards from Amgen, Sanofi, Regeneron, Gemphire, Kowa and Arrowhead. ST is a co-inventor, receives royalties from patents owned by the University of California San Diego on oxidation-specific antibodies, is a co-founder of Oxitope, Inc and Kleanthi Diagnostics and currently has a dual appointment at UCSD and Ionis Pharmaceuticals. PTK has received consultancy fees, lecture honoria and/or travel fees from Amgen, AstraZeneca, MSD Finland, Raisio Group, Sanofi.

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